organized into different discrete niches each with unique characteristics including enrichment for specific cell populations. B cell were often organized into large clusters with CD4 T cells including T follicular helper-like cells. In contrast, the CD4- T cell populations formed small dispersed clusters which, on a per patient basis, predicted progression to ESRD (p=0.004).

Conclusions These data reveal that in LN, specific *in situ* inflammatory states are associated with the failure of conventional therapy and progression to ESRD.

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505 PARENCHYMAL INFγ RESPONSE REGULATES MURINE LUPUS NEPHRITIS

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Background Lupus nephritis is the most common life-threatening end-organ complication of SLE. Interstitial infiltrates, specifically T cells, are major predictors of disease outcomes. We recently determined that kidney-infiltrating T cells (KITs) are suppressed after kidney infiltration and exhibit an exhausted phenotype. Notably, the kidneys of nephritic lupus-prone (MRL.*Fas*^{lpr}) mice upregulate PD-L1, which we hypothesize is one mechanism inducing KIT suppression. IFNγ is the major inducer of PD-L1 and given the known role of IFNγ in lupus nephritis, we postulated that IFNγ induces a protective program in the kidneys of lupus-prone mice, in direct contrast to the proinflammatory role of IFNγ in the hematopoietic compartment.

Methods MRL. *Fas*^{lpr} mice develop autoantibodies, proteinuria, dermatitis, and glomerulonephritis. Others have previously shown that global IFNγ receptor deficiency (IFNγR$^{-/-}$) ameliorates disease in this mouse model. To determine if IFNγ signaling on parenchymal cells regulates disease, we generated bone marrow chimeras by transferring congenically labeled WT immune cells into either wild-type (WT) or IFNγR$^{-/-}$ MRL.*Fas*^{lpr} recipients. If our hypothesis is correct, then the IFNγR-/- recipients would have more severe disease than their WT counterparts. Chimerization occurred at 4-6 weeks of age and female and male mice were analyzed for disease pathology at 23 and 27 weeks post-chimerization respectively. Analysis included proteinuria, renal histology for both interstitial and glomerular disease, dermatitis, autoantibody production, and immune cell activation. Survival analysis was performed on female mice. Additional analysis focused specifically on T cell phenotypes.

Results IFNγR$^{-/-}$ MRL.*Fas*^{lpr} recipient mice exhibited more severe and rapid disease onset than WT recipient controls. While proteinuria was not different between the two groups, the IFNγR$^{-/-}$ recipients had more severe glomerulonephritis (p< 0.005) and interstitial disease (p< 0.001). Consistent with these findings, IFNγR$^{-/-}$ recipients had reduced survival (p< 0.05). As expected, IFNγR deficiency resulted in reduced PD-L1 expression. When examining infiltrates, KITs isolated from IFNγR$^{-/-}$ recipients exhibited increased expression of Tim3 and PD-1.

Conclusions These experiments suggest that parenchymal IFNγR signaling results in upregulation of protective mechanisms which reduce kidney disease and alter T cell phenotypes. This contrasts with global IFNγR$^{-/-}$ which ameliorated kidney disease. Overall, this finding argues that suppression of IFNγ, and possible other inflammatory mediators, may have differential effects on specific cell lineages and that global suppression of IFNγR may have both positive and negative effects on disease pathogenesis. This will need to be considered when devising targeted therapies.

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506 BELIMUMAB (BEL) IMPROVES RENAL OUTCOMES IN ACTIVE LUPUS NEPHRITIS (LN): A PHASE 3 RANDOMIZED, PLACEBO (PBO)-CONTROLLED TRIAL

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Background BEL is approved for patients (pts) with systemic lupus erythematosus (SLE). We evaluated intravenous (IV) BEL in active LN.

Methods This 104-week trial (GSK Study BEL114054; NCT01639339) randomized adults with active LN (class III, IV, and/or V) 1:1 to monthly BEL 10 mg/kg IV or PBO, plus standard therapy (ST) with high-dose corticosteroids + either cyclophosphamide (CyC) or mycophenolate mofetil (MMF) for induction at the investigator's discretion. CyC was followed by azathioprine (AZA), and MMF by MMF maintenance. The primary endpoint was Primary Efficacy Renal Response (PERR = urine protein:creatinine ratio [uPCR] ≤0.7; estimated glomerular filtration rate [eGFR] no more than 20% below pre-flare value or ≥60 ml/min/1.73m^2; no rescue therapy) at Week 104. Other endpoints were Complete Renal Response (CRR = uPCR <0.5; eGFR no more than 10% below pre-flare value or ≥90 ml/min/1.73 m^2; no rescue therapy) at Week 104; time to renal event (end-stage kidney disease, doubling of serum creatinine, increased proteinuria and/or impaired renal function, renal disease-related treatment failure) or death. Endpoints were analyzed by ST regimen.

Results 224 pts were randomized to each arm. At Week 104, there were significantly more PERR and CRR responders on BEL vs PBO: (43.0% vs 32.3%, OR [95% CI] 1.6 [1.0, 2.3]; p=0.03) and (30.0% vs 19.7%, OR [95% CI] 1.7 [1.1, 2.7]; p=0.02), respectively. Risk of renal event or death was lower in BEL pts relative to PBO (HR [95% CI] 0.5 [0.3, 0.8]; p<0.01). Week 104 PERR response rates in pts on CyC/AZA were 33.9% with BEL and 27.1% with PBO, and 46.3% with BEL vs 34.1% with PBO in those on MMF. BEL reduced risk of renal event or death on background of CYC/AZA (HR [95% CI] 0.5 [0.2, 1.0]) and MMF (HR [95% CI] 0.5 [0.3,